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| **In re Application of:** Hans GROENLUND et al. | : | **Confirmation No.:** 9022 |
| **Serial No.:** 10/510,655 | : | **Group Art Unit:** 1644 |
| **Filed:** November 30, 2004 | : | **Examiner:** N. ROONEY |

**For:** MICROPARTICLES COMPRISING CARBOHYDRATE BEADS COVALENTLY LINKED WITH ALLERGEN

**Attorney Docket No.:** LNK-031

Mail Stop **AMENDMENT**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

## DECLARATION UNDER 37 C.F.R. 1.132

I, Professor Rudolf VALENTA, am a professor at the Division of Immunopathology (Department of Pathophysiology, University of Vienna, Austria) and I do hereby declare and state that:

1. I studied medicine at the University of Vienna and graduated with an MD degree in 1987. I have extensive training in molecular biological techniques, cellular mouse immunology, internal medicine, and clinical study design. I was granted a specialist degree for pathophysiology in 1996, and in 1997, I completed my specialist training in immunology and became associate professor for Pathophysiology.

2. Since 1988, I have worked at the Department of Pathophysiology (formerly Department of General and Experimental Pathology) at the University of Vienna, Austria. In 1992, I was awarded the qualification of a university lecturer for general and experimental pathology and became Head of the Molecular Immunopathology group at the Division of Immunopathology. I

have been Head of the Division of Immunopathology since 2001. During my tenure as Division Head, I have directed a specialist research program directed to the study of molecular and immunological strategies for prevention, diagnosis, and treatment of Type I allergies.

3. I have contributed to more than 300 peer-reviewed scientific papers, reviews, and book chapters. My pioneering work on the characterization of allergens and their use for new concepts of allergy treatment was granted numerous scientific awards, the following among others: the Sandoz Austria Award for Biology in 1994, the International Award of the Pharmacia Allergy Research Foundation in 1996, the START Award of the Austrian Science Fund in 1998, and the Sarsedt Science Award in 2000.

4. I am a co-inventor, along with Hans GROENLUND (also known as Hans GRÖNLUND), Johan ROENNELID (also known as Johan RÖNNELID), Alex KARLSSON-PARRA, Marianne VAN HAGE-HAMSTEN, Susanne VRTALA, Ursula WIEDERMANN, and Dietrich KRAFT, of the subject matter described and claimed in the above-referenced patent application.

5. I am familiar with the above-referenced patent application, including the pending claims and the Non-Final Office Action issued on May 29, 2009, as well as the proposed amended claims filed concurrently herewith. It is my understanding that all pending claims stand rejected as lacking adequate enablement and written description.

6. With regard to enablement, it is my understanding that the Examiner finds the specification adequately teaches one of skill in the art how to make and use a microparticle consisting essentially of the timothy grass pollen allergen Phl p 5b covalently bound to a cyanogen bromide-activated spherical sepharose particle (i.e., the CBP-rPhl p 5b of the disclosed examples) but fails to teach the therapeutic use of other embodiments, including (a) the use of other agarose

beads and (b) the use of other plant pollen allergens.

7. It is my understanding that the test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent application coupled with information known in the art at the time of invention without undue experimentation.

8. On the issue of "how to make" the particles and medicaments of the pending claims, it is my informed opinion that the covalent coupling of recombinant polypeptide allergens to carbohydrate particles, such as agarose beads, utilizes well-described, routine, and reproducible procedures known at the time of invention in the context of immunoassays to provide high density, high yield, and stable bonding, all while preserving the immunological properties of the conjugated allergens. As such, one of skill in the art at the time of invention would have been fully capable of manufacturing embodiments of the present invention without undue experimentation.

9. On the issue of "how to use" the medicaments of the pending claims in the context of allergen-specific immunotherapy (ASIT), it is my informed opinion that results of record, including those presented herewith in Appendices A and B and summarized in Appendix C, support the premise of the invention that carbohydrate-based particles ("CBPs") may be readily and routinely substituted for conventional aluminium-hydroxide as a vaccine adjuvant useful in the context of allergen-specific immunotherapy (ASIT) with predictable and beneficial results. Given the well-established equivalence and alternative nature of recombinant allergens and their respective natural counterparts in the context of immune responses and ASIT, respectively,[1] it is my informed opinion that one of ordinary skill would reasonably expect further combinations of the

[1] See the enclosed abstracts of the articles by D. Kraft et al., "The Importance of Recombinant Allergens for Diagnosis and Therapy of IgE-Mediated Allergies", Int Arch Allergy Immunol, (1999) vol. 118: 171-176 and R. Valenta et al., "Recombinant Allergens for Immunology", J Allergy Clin Immunol

present invention to indeed be "capable of inducing a strong allergen-specific IgG response comparable to that of an equivalent Alum-bound allergen with less granulomatous tissue reactions as compared to said Alum-bound allergen." Furthermore, given the high level of skill of the ordinary artisan, the ample direction and guidance provided by the instant disclosure, and the routine and conventional nature of the requisite comparative and confirmatory protocols, it is my informed opinion that any experimentation needed to determine whether a particular combination indeed meets this criteria cannot be fairly characterized as "undue."

10. With regard to the written description rejection, it is my understanding that the Examiner has found Applicants to be in possession of a timothy grass pollen allergen Phl p 5b covalently bound to a cyanogen bromide-activated spherical sepharose particle (i.e., the CBP-rPhl p 5b of the disclosed examples) but not in possession of the broader genus, including medicaments composed of other agarose beads and other plant pollen allergens.

11. It is my understanding that a specification may, within the meaning of 35 U.S.C. § 112, first paragraph, contain a written description of a broadly claimed invention without describing each and every species that the claim encompasses and that the test for adequacy of the written description is whether the originally filed application reasonably conveys to a person of ordinary skill in the art that Applicants were in possession of the presently claimed subject matter, including the limitations in question.

12. Upon information and belief, it is my informed opinion that the evidence of record--summarized in Appendix C provided herewith--supports Applicants' position that the presently claimed genus of ASIT medicaments, consisting essentially of agarose-plant pollen allergen microparticles, lacks substantial

(2007), vol 119 (4): 826-830.

variation and thus is adequately represented by the CBP-rPhl p 5b species described in the instant specification, with the rPhl p 5b polypeptide being sufficiently representative of the common attributes or features of the established class of "recombinant polypeptide allergens derived from plant pollen" and cyanogen bromide-activated spherical Sepharose (also known as "beaded agarose") being sufficiently representative of the common attributes or features of the established class of "three dimensionally cross-linked agarose beads." As such, it is my informed opinion that the originally filed application reasonably conveys to a person of ordinary skill in the art that Applicants were in possession of the presently claimed subject matter, including the limitations in question.

13. Based on my review of the prosecution history to date, it appears that the Examiner's enablement and written description concerns center on whether one of skill in the art could reasonably extrapolate from the examples of the instant disclosure to the breadth of the pending claims. To demonstrate the wide applicability of the invention of the pending claims, my colleagues and I undertook studies to confirm that carbohydrate-based particles ("CBPs"), particularly agarose particles, are useful as vaccine adjuvants in combination with allergens other than the recombinant timothy grass allergen, Phl p 5b (SEQ ID NO: 1), of the instant disclosure. The detailed protocol and associated results set forth in Appendices A and B provided herewith strongly support the broad utility and operability of the agarose-plant pollen allergen particles of the present claims as medicaments for allergen-specific immunotherapy (ASIT).

14. Appendix A describes the routine construction and study of an embodiment of the present invention, namely a G-CBP vaccine for grass pollen allergy composed of a previously described recombinant hybrid molecule ("G-antigen") consisting of the major grass pollen allergens Phl p 1, Phl p 2, Phl p 5, and Phl p 6 (1) coupled to cross-linked agarose beads pre-activated with N-hydroxysuccinimide and formulated to a vaccine ("G-CBP"). As the results

in Appendix A bear out, immunization of BALB/c mice with the G-CBP vaccine yielded both a pronounced allergen-specific $IgG_1$ response (Figure 1) and a pronounced allergen-specific T-cell response (Figure 2). These findings strongly support the utility and operability of G-CBP, a species falling within the genus of the pending claims, as a medicament for allergen-specific immunotherapy (ASIT).

15. Appendix B describes the routine construction and study of an embodiment of the present invention, namely an F1+F2-CBP vaccine for grass pollen allergy composed of two recombinant hypoallergenic derivatives of the major birch pollen allergen, Bet v 1 (i.e. Bet v 1F1 and Bet v 1F2) coupled to cross-linked agarose beads, pre-activated with N-hydroxysuccinimide and formulated to a vaccine ("F1+F2-CBP"). As the results in Appendix B bear out, immunization of BALB/c mice with the G-CBP vaccine not only yielded a pronounced allergen-specific $IgG_1$ response comparable to that of the aluminum hydroxide-adsorbed rBet v 1 vaccines studied by Pauli et al. (JACL (2008), vol. 122(5): 957), but also resulted in reduced inflammatory reaction and granulomatous response as compared to an Alum-based equivalent. These findings strongly support the utility and operability of F1+F2-CBP, a species falling within the genus of the pending claims, as a medicament for allergen-specific immunotherapy (ASIT).

16. The findings of Theresa Neimert-Andersson (Allergy (2008), vol. 63: 518-526, of record) further support the proposition that carbohydrate-based particles ("CBPs") may be readily substituted for conventional aluminium-hydroxide as vaccine adjuvant in the context of allergen-specific immunotherapy (ASIT) with predictable and beneficial results. As the instant disclosure accurately predicts, immunization of BALB/c mice with CBP-rFel d 1 particles yielded pronounced allergen-specific IgG and $IgG_2$ responses that correlate to the presence of blocking antibodies and correlate to clinical efficacy the context of ASIT.

17. In summation, it is my informed and expert opinion that one of ordinary skill in the art would not find the principles of the instant invention to be limited to a particular CBP or a particular allergen, but instead to be readily and routinely extrapolated and generalized for a wide range of combinations, thereby providing ample enablement and written description of the full scope of the pending claims.

18. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Prof. RUDOLF VALENTA, MD

**Date:** 14.1.2010

**Professor Rudolf VALENTA**